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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/841,843	04/25/2001	Jurgen Bode	BOET 0130 PUS	6703

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WILLIAM G. CONGER
Brooks & Kushman P.C.
22nd Floor
1000 Town Center
Southfield, MI 48075-1351

EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

8/M

Office Action Summary	Application No.	Applicant(s)	
	09/841,843	BODE ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4, 6-10, 12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-10, 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 10, 2003 has been entered.

DETAILED ACTION

This application filed April 25, 2001, is a continuation of application 09/257,561, filed February 25, 1999, now abandoned, which claims benefit to foreign application 98 103 490.3 filed February 27, 1998 with the EPO.

Applicants amendment filed March 12, 2004, has been received and entered. Claim 11 has been cancelled. Claim 12 has been added. Claims 1-4, 6-10 and 12 are pending.

Election/Restriction

Applicant's election of Group I, claims 1-4, 6, 10 in Paper No. 6 was acknowledged. Because, the election and was treated as an election without traverse because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement (MPEP § 818.03(a)). Applicant has not provided any new arguments, therefore the restriction is maintained for the reasons of record. Review of newly added claim 12 indicates that it belongs to the elected group. Accordingly, it will be examined with the elected invention.

Claims 1-4, 6-10, and 12 are pending. Claims 7-9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 6. Claims 1-4, 6, 10 and 12 are currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 10 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use of a FLP/frt recombinase system in a mouse embryonic stem cell comprising the specific method steps set forth in claim 1 for the generation of a transgenic mouse, does not reasonably provide enablement for use of embryonic stem cells from other vertebrates for the generation of transgenic vertebrates is withdrawn.

The amendment to the claims has obviated the basis of the rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6-10 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, step (d) of claims 1 and 12 is unclear because to maintain conditions of positive selection, step (b), the cells must have the selectable marker

otherwise there is no selection. If the selection conditions are maintained once the first expression cassette containing the positive selectable marker as required by step (d) it is unclear how such a selection could occur. The claim is unclear because loss of a selectable marker during the exchange appears to preclude continuation of selection conditions. It is unclear when the positive selection step should be halted, throughout the exchange period or until the exchange of the first and second cassette is started. More clearly setting forth the time or conditions of step (d) will obviate the basis of the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6 rejected under 35 U.S.C. 102(b) as being anticipated by Schlake *et al.* (Biochemistry, 1994) is withdrawn.

Applicants summarize the basis of the rejection, reviewing the general teaching of Schlake *et al.* and argue that Schlake *et al.* explicitly decide not to use embryonic stem cells because of art recognized drawbacks and reduce to practice instead an established cell line which has lost its ability to affect homologous recombination as compared to embryonic stem cells (pages 5-7). Further it is argued that Schlake *et al.* do not teach step (d) of claim 1 (pages 7-8).

See Applicants' amendment, pages 5-8, section A. Applicants' arguments have been fully considered, and found persuasive.

Examiner would agree that Schlake *et al.* does not specifically teach to use ES cells in combination of the vector system, rather it is taught that the system can be used in cells that have less of a capacity of homologous recombination than ES cells. Because Schlake *et al.* does not specifically teach to use ES cells each of the embodiments of the claimed invention are not anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlake *et al.* (Biochemistry, 1994).

Applicants have not argued that the vector system used by Schlake *et al.* is different from that disclosed and claimed in the present specification. A comparison of the specific positive and

negative markers and specific recombinase sites reduced to practice in both the present disclosure and Schlake *et al.* indicate the vector and methodology used for selecting exchanged sequences are the same.

To the extent that Applicants arguments apply to the instant rejection Applicants would maintain that Schlake *et al.* does not explicitly decide not to use embryonic stem cells because of art recognized drawbacks and reduce to practice instead an established cell line which has lost its ability to affect homologous recombination as compared to embryonic stem cells (pages 5-7). See Applicants' amendment, pages 5-8, section A.

Examiner would agree that Schlake *et al.* does not specifically teach to use ES cells in combination of the vector system, rather it is taught that the system can be used in cells that have less of a capacity of homologous recombination than ES cells. However, Schlake *et al.* teach that the skilled artisan uses embryonic stem cells for targeted integration and it is well known in the art that mouse embryonic stem cells are used in the generation of transgenic mice. Again, there is no teaching in Schlake *et al.* that embryonic stem cells would not work in the instantly claimed method, and it seems that Applicants are relying on the fact that Schlake *et al.* chose to reduce to practice the claimed invention in a cell type which would be less effective in homologous recombination. Applicants' arguments would not be not found persuasive because Schlake *et al.* discuss the use of targeted homologous recombination in embryonic stem cells and there is no specific teaching of limitations or characteristics taught to using embryonic stem cells which would prohibit there use in the instantly claimed method. On the contrary, it would be obvious to one of skill in the art at the time of the claimed invention to use a vector system specifically taught to be used for homologous recombination in methodology that requires such

vectors. Schlake *et al.* demonstrate the power of the vector system in cell lines that have a lower capacity for homologous recombination than ES cells. Homologous recombination in is ES cells is greater that most cell types, however the frequency is not high, therefore, one of skill in the art would be motivated to use vectors and methodology that would increase the chances of obtaining clones that have successfully undergone homologous recombination. Again, there is no specific teaching away in from using embryonic stem cells nor specific teaching that embryonic stem cells have characteristics or limitations which would make them non-functional in the current methods. Moreover, since embryonic stem cells may be expected to have an increased capacity for recombination they may provide increased efficiency of the method.

Therefore, because Schlake *et al.* teach the same vector system and teach limitation encompassed by the instantly claimed method Schlake *et al.*

Claims 1, 10 and 11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Schlake *et al.* in view of Jung *et al.*

Claims 1, 10 and 11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Schlake *et al.* in view of Ludwig *et al.*

Applicants summarize the basis of the rejections and outline the requirements for making a *prima facie* case of obviousness (pages 8-9). Applicants argue that none of the reference specifically teach the selection conditions required by step (d) of claim 1 (page 10). Again, Applicants argue that Schlake *et al.* 'clearly states not use embryonic stem cells but rather suggests to use established cell lines like BHK or CV-1 cells due to their known advantages' (bottom of page 10). Further, because of this negative teaching by Schlake *et al.* one of skill in

the art would not combined the teaching of Jung *et al.* and/or Ludwig *et al.* for the generation of a transgenic mouse, and that the methods taught by Jung *et al.* and Ludwig *et al.* are different from those instantly claimed (pages 10-11. Finally, Applicants argue that the presently claimed invention provides surprising results which could not have been predicted by the work of Schlake *et al.* (page 11). See Applicants' amendment, pages 8-11, Section 2. Applicants' arguments have been fully considered, but not found persuasive.

As noted above, the vector system taught by Schlake *et al.* is the same as reduced to practice in the instant disclosure and the methods taught by Schlake *et al.* Examiner concedes that Schlake et al. does not specifically teach to use the recombination system for ES cells, however as argued above this would be obvious to one of skill in the art at the time of filing of the claimed invention. At the time of filing it is well known in the art that mouse embryonic stem cells are routinely used for targeted recombination and subsequently used to generate transgenic mice. As illustrated by the teaching of Jung *et al.* and Ludwig *et al.* teach the specific methodology required for generating transgenic mice and as evidence that known recombinases are used and functional within the context of the claimed invention. Applicants' arguments are not found persuasive because the teaching of Schlake *et al.* makes obvious claim 1 and the use of embryonic stem cells. Moreover, the routine use of mouse embryonic stem cells for the targeted recombination of a gene of interest for the specific purpose of generating the transgenic mouse. The test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art *(In re McLaughlin,* 443 F.2d 1392, 170 USPQ 209 (CCPA 1971)) and for the purpose of combining references, those references need not explicitly suggest combining

teachings, much less specific references (*In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988)). At the time of filing the use of use of mouse embryonic stem cells for the generation of transgenic mice was well known and routine. Additionally, positive/negative selection vectors and methods using these vectors were routinely used for affecting homologous recombination in embryonic stem cells. Further, the use of recombinases in the targeting vectors and resulting cell were also used. Given the teaching by Schlake *et al.* that the vectors and methods taught therein provide methodology for targeted recombination which is effective in cells which are perceived to have a lower capacity for homologous recombination than embryonic stem cells provides clear motivation for using this more effective methodology. Moreover, the successful results of each of references provide a clear expectation of success.

With respect to the claimed invention giving unexpected results, Examiner agrees that the limitations set forth in claim 12 would not have been obvious bases on the art of record, and therefore is not included in the basis of the rejection. However, the remaining claims set forth no such limitation to differentiate the claimed invention or to embodiments that are unexpected from that made obvious by the prior art. Applicants' arguments are not found persuasive because Schlake *et al.* make obvious the method of claim 1, and the use of mouse embryonic stem cells for the generation of transgenic mice would have been obvious and would have had a high expectation of success for this use.

Therefore, for the reasons stated above and in the previous office action the rejections are maintained.

Conclusion

Claim 12 is free of the art of record because the art fails to teach that using the F3 FRT site sequence would result in at least a 25% recombination frequency as required by the instant claims. While multiple FRT sites have been used, there was no specific teaching that the use of F3 would result in the frequency required by the instant claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (571) 272-0734.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach

Joe Woitach

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